Ginekol Pol. 2011, 82, 840-844

Dietary antioxidant levels in hyperemesis gravidarum: A case control study

Poziom antyoksydantów a wymioty ciężarnych – badanie porównawcze przypadków

Celik Fatma[1], Guzel Ali Irfan[2], Kuyumcuoglu Umur[3], Çelik Yusuf[4]

[1] - Dicle University School of Medicine, Department of Public Health, Turkey,
[2] - Ergani State Hospital, Obstetrician and Gynecologist, Turkey,
[3] - Dicle University School of Medicine, Former Head of Obstetrics and Gynecology Department, Diyarbakir, Turkey,
[4] - Dicle University School of Medicine, Department of Bioistatistics and Medical Informatics , Diyarbakir, Turkey,

Abstract

Objectives: *Dietary antioxidant intake decreases the risk of many diseases. Hyperemesis gravidarum (HG) is the most common eating disorder during pregnancy. Therefore, the authors conducted this prospective and case control study to evaluate dietary antioxidant levels of women with HG and compare with healthy pregnant women.*

Material and Methods: *This prospective case control study was conducted at a government hospital in the southeastern region of Turkey, from February 2010 to May 2010. A total of 100 pregnant women were included into the study. Dietary antioxidant levels (DAL) were measured according to the new 92-item antioxidant nutrient questionnaire developed by Satia et al (1). 50 women with HG and 50 healthy pregnant women were evaluated. Statistical analyses were carried out with statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).*

Results: *There were no statistically significant differences between the groups regarding the age of the patients, gestational age, educational status, body height and weight ($p>.05$). Vitamin E, E equivalent, vitamin C, carotene and vitamin A levels were significantly lower in women with HG ($p<.05$). The results of logistic regression method for these variables including odds ratio (95 % CI) were as follows: 10.07(1.52-66.51), 7.37(2.66–20.41), 4.26(2.66–20.41), 3.66(2.38–5.63) and 2.75 (1.56–4.85), respectively.*

Conclusion: *According to this study, vitamin E, E equivalent, vitamin C, carotene and vitamin A levels of women may play a role in the pathogenesis of HG. Therefore, diet recommendations should be given by clinicians before pregnancy.*

Key words: **dietary antioxidant levels** / **hyperemesis gravidarum** / / **nutrient questionnaire** /

Corresponding author:
Ali Irfan Guzel
Mega Center Karsisi, Polis Loj. Sok., Murat 6 Apt., Kat:6 No:25, 21280, Diyarbakir, Turkey
tel: +90 412 248 80 01
fax: +90 412 248 80 12
e-mail address: alijnk@hotmail.com

Otrzymano: **25.08.2011**
Zaakceptowano do druku: **20.10.2011**

Streszczenie

Cel: *Spożywanie antyoksydantów obniża ryzyko wielu chorób. Wymioty ciężarnych (HG) są najczęstszym zaburzeniem odżywiania w ciąży. Z tego powodu autorzy przeprowadzili badanie porównawcze przypadków celem oceny poziomu antyoksydantów u kobiet z wymiotami ciężarnych w porównaniu ze zdrowymi kobietami.*

Materiał i metody: *Badanie przeprowadzono w szpitalu w południowowschodniej Turcji, w okresie od lutego 2010 do maja 2010 na 100 ciężarnych kobietach. Poziom antyoksydantów (DAL) mierzono według nowego 92 pytaniowego kwestionariusza dotyczącego spożycia antyoksydantów opracowanego przez Satia [1]. Oceniono 50 ciężarnych z wymiotami i 50 zdrowych ciężarnych. Analizę statystyczną przeprowadzono przy pomocy pakietu statystycznego SPSS 15.0 dla Windows (SPSS Inc., Chicago, IL, USA).*

Wyniki: *Nie znaleziono istotnych statystycznie różnic pomiędzy badanymi grupami w odniesieniu do wieku pacjentek, wieku ciążowego, wykształcenia, wzrostu i wagi (p>0,05). Poziomy witaminy E, równoważnika wit. E, witaminy C, karotenu, i witaminy A były istotnie niższe u ciężarnych z wymiotami (p<0,05). Wyniki regresji logistycznej dla tych zmiennych włączając iloraz szans (95% CI) wynosiły odpowiednio: 10,07(1,52–66,51), 7,37(2,66–20,41), 4,26(2,66–20,41), 3,66(2,38–5,630) i 2,75(1,56–4,85).*

Wnioski: *Witamina E, równoważnik wit. E, witamina C, karoten i witamina A może odgrywać istotną rolę w patogenezie wymiotów ciężarnych. Lekarze klinicyści powinni dawać zalecenia dietetyczne kobietom przed zajściem w ciążę.*

Słowa kluczowe: **poziom antyoksydantów** / **wymioty ciężarnych** / / **kwestionariusz odżywiania** /

Introduction

Hyperemesis gravidarum (HG) is the most common and severe form of nausea and vomiting of pregnancy, with an incidence of 0.3–1.5 % of all live births.

HG is characterized by intractable and treatment-resistant nausea and vomiting, resulting in electrolyte imbalance, nutritional deficiency and weight loss [1]. HG is more common in multiple gestations and gestational trophoblastic disease [2]. In severe cases, HG causes complications such as Wernicke's encephalopathy, central pontine myelinolysis, vasospasm of cerebral arteries, rhabdomyolysis, coagulopathy and peripheral neuropathy. However, prompt and appropriate intravenous fluid therapy, vitamin supplementation and electrolyte imbalance correction may prevent symptoms and complications [3].

For some time diet has been believed to play a role in the development of chronic diseases such as cancer, coronary heart disease, obesity, diabetes type 2, hypertension and cataract. A diet containing high antioxidant levels, particularly a plant-based one, reduces the risk of the development of such diseases [4]. The mechanism of this protection depends on the protective role of the antioxidant defense by inhibiting reactive oxygen species (ROS) [5]. Wang et al., have shown that during pregnancy maternal stress increases and leads to excessive production of ROS [6]. Previous studies reported that maternal oxidative stress leads to pregnancy complications and vitamin supplementation of A, C and E plays a role in fetal growth [7, 8].

Our aim was to perform a case control study to evaluate the DAL in HG, the most common eating disorder in pregnancy, by using the new 92-item antioxidant nutrient questionnaire.

Materials and Methods

Study Design and Participants

This prospective case control study was conducted at Ergani Government Hospital, Department of Obstetrics and Gynecology, from February 2010 to May 2010. This is a secondary hospital in the southeastern region of Turkey. This is a government-supported hospital and most of the health services are free of charge, therefore, the socioeconomic status of the patients is mostly low. A total of 100 pregnant women were included into the study, all of them of Turkish nationality, non-smokers, with no history of alcohol or drug use. 50 patients had HG (the study group) and 50 had normal healthy pregnancies (the control group). HG was defined as severe nausea and vomiting in pregnancy, requiring treatment with IV fluids and/or parenteral nutrition. All pregnancies were accurately calculated by the last menstrual period and/or by first-trimester ultrasonographic (Shimadzu SDU-2200 PRO) investigation. The study was performed according to the standards of Helsinki declaration, and written informed consent was obtained from all participants.

Data Collection

Upon admission, all participants were informed about the study. Dietary antioxidant levels (DAL) were measured according to the new 92-item antioxidant nutrient questionnaire developed by Satia et al [1]. Clinical information obtained from the patients included age, education status, gravidity, parity, gestational weeks, height-weight (body mass index [BMI; calculated as kg/m^2], blood pressure, smoking and thyroid function tests. Respondents with higher educational status completed the questionnaire by themselves. In cases of patients with lower educational status, an appointed nurse, the same person in each case, helped the subjects to complete the questionnaire.

Antioxidant Nutrient Questionnaire

Dietary antioxidant levels (DAL) were measured according to the new 92-item antioxidant nutrient questionnaire developed by Satia et al., [1], modeled after the semi-quantitative FFQ (Food Frequency Questionnaire) and designed to capture usual dietary and supplemental intakes of carotenoids, vitamin C, and vitamin E. The pregnant women were asked how often they ate particular foods over the course of the past month and also to mark the amount of each food they ate as 'small', 'medium' or 'large'.

Nutrient analyses were performed with the use of the nutrient database program (BeBiS software program) designed to evaluate Turkish and commercial foods [9].

Statistical Analyses

The mean difference and standard deviations (SD) were calculated for continuous variables. Subject characteristics and demographics were analyzed descriptively. The normal distribution of the variables was analyzed by the Kolmogorov–Smirnov test. The Chi-square (χ^2) test and the Student's *t*-test were used to evaluate associations between the categorical and continuous variables. The logistic regression method was used to find the risk variables for specific nutrients by including all variables in the model and to calculate the odds ratio. The receiver operator characteristic (ROC) curve analysis was used to establish the cutoff values for vitamin E, vitamin E equivalent, vitamin C, carotene and vitamin A levels.

Results

The demographic and clinical characteristics of the cases are shown in table I.

We evaluated 50 HG pregnant cases and 50 pregnant controls. The mean age of the respondents in the HG and the control groups were; 26.36±5.63 years and 25.09±4.84 years, respectively (p=0.229). Mean gestational weeks of the fetuses were 7.32±1.14 weeks in the HG group and 7.64±0.97 weeks in the control group (p=0.134). There were no significant differences in maternal and gestational age between the groups. The BMI of the HG group and the control group were 25.02±2.61 mg/m^2 and 25.23±2.90 mg/m^2, respectively (p=0.704). There was no statistically significant difference regarding systolic and diastolic blood pressures between the groups (p>0.05). 12 cases had hyperthyroidism, 9 (75 %) of which were in the HG group. The hyperthyroid cases had anti-thyroid therapy.

Vitamin E, E equivalent, vitamin C, carotene and vitamin A levels were statistically significantly different between the groups. The levels of these nutrients are depicted in table II.

All of these nutrients were found to be lower in the HG group. Table III summarizes the outcomes of the logistic regression model. According to the model, the highest difference was in vitamin E, followed by vitamin E equivalent, vitamin C, carotene and vitamin A levels with odd ratios (95%CI) as follows: 10.07(1.52-66.51), 7.37(2.66-20.41), 4.26(2.66-20.41), 3.66(2.38-5.63) and 2.75(1.56-4.85), respectively.

Table I. Clinical and demographic characteristics of the pregnant women.

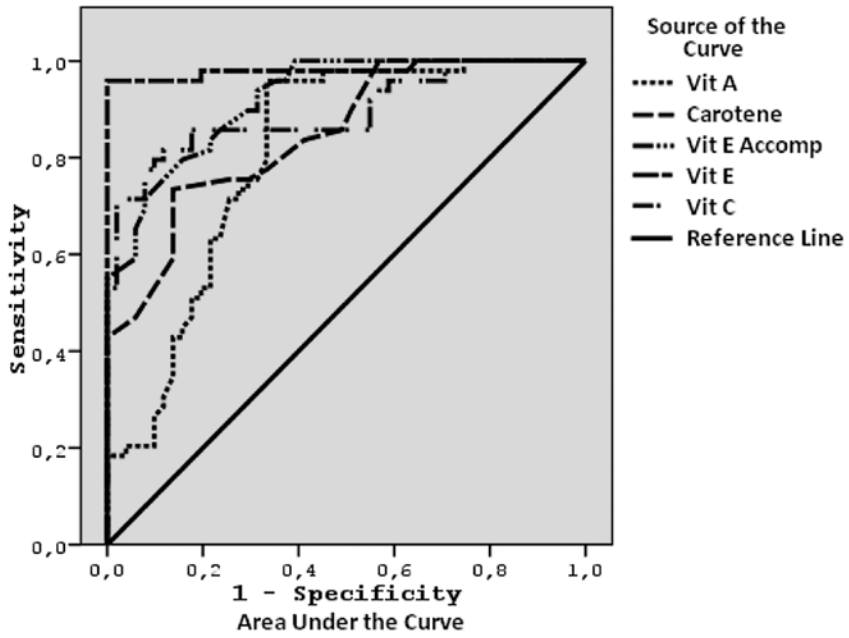
	Pregnant with hiperemesis gravidarum (n=50)	Pregnant with normal pregnancy (n=50)	Test values
Age (years)	26.36±5.63	25.09±4.84	t=.900;p=0.229
Gravidity ≤3 (%)	41(82)	34(68)	χ^2=8.492;p=0.131
Gestational weeks	7.32±1.14	7.64±0.97	t=-1.510;p=0.134
BMI (kg/m^2)	25.02±2.61	25.23±2.90	t=-0.380;p=0.704
Systolic blood pressure (mmHg)	119,28±11,03	122,74±12,13	t=-1.489;p=0.104
Diastolic blood pressure (mmHg)	74.89±8.50	75.68±8.36	t=-0,467;p=0.641
Educational status (n)*			
No education	33	36	χ^2=0.320;p=0.571
Primary school	17	14	

Table II. The levels of antioxidants between the groups.

Nutrients	Pregnant with hiperemesis gravidarum (n=50)	Pregnant with normal pregnancy (n=50)	Test values
Vitamin E (µg)	174,59±97,31	4.09±4.19	t=12.503;p<0.01
Vitamin E equivalent (µg)	5.48±1.75	2.68±1.14	t=9.466;p<0.001
Vitamin A (µg)	686.13±55.32	1589.38±412.58	t=2.213;p=0.029
Vitamin C (µg)	598,70±376.24	104.52±92.69	t=9.099;p<0.001
Carotene (mg)	1.55±0.85	0.62±0.43	t=6.925;p<0.001

Table III. Results of logistic regression method and odd ratios of the nutrients.

Variables	β*	S.E.	Wald	p	OR(%95 CI)
Vitamin E	2.31	0.96	5.75	0.021	10.07(1.52-66.51)
Vitamin Eq	1.99	0.52	14.74	<0.001	7.37(2.66-20.41)
Vitamin C	1.45	0.42	11.91	0.001	4.26(2.66-20.41)
Carotene	1.29	0.22	34.76	<0.001	3.66(2.38-5.63)
Vitamin A	1.01	0.29	12.12	<0.001	2.75(1.56-4.85)



Area Under the Curve

Test Result Variable(s)	Area	S.E	p	Asymtotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Vit A	.809	.044	<.001	.722	.896
Carotene	.849	.037	<.001	.777	.922
Vit E Accomp	.922	.024	<.001	.874	.970
Vit E	.983	.014	<.001	.956	1.000
Vit C	.894	.033	<.001	.829	.959

S.E: Standard Error
p: Significant level

Figure 1. Receiver operating characteristic (ROC) areas under the curves (AUC) of vitamin A, carotene, vitamin E equivalent, vitamin E and vitamin C.

Receiver operating characteristic (ROC) areas under the curves (AUC) of vitamin A, carotene, vitamin E equivalent, vitamin E, vitamin C are shown in Figure 1.

The AUCs (95 % CI) for these nutrients were 0.809 (0.722-0.896), 0.849 (0.777-0.922), 0.922 (0.874-0.970), 0.983 (0.956-1.000) and 0.894 (0.829-0.959), respectively.

Discussion

Hyperemesis gravidarum is an eating disorder of pregnancy that is characterized by intractable nausea and vomiting leading to fluid, electrolyte and acid-base imbalance, nutrition deficiency and weight loss [10]. HG also increases the risk of fetal complications such as spontaneous abortion and fetal demise due to undernutrition and hypovitaminosis [11].

Diet has been believed to play a role in the development of chronic diseases and literature has been reporting a connection between the diet and the diseases [12- 14]. Cell damage caused by ROS is considered to result in degenerative diseases of aging such as cancer, cardiovascular disease, cataracts, immune system decline, and brain dysfunction [15]. Antioxidants are the elements that are known to control the formation of the ROS and prevent cell damage [5]. Vitamin C, vitamin E, vitamin A and beta carotene are the best known dietary antioxidants [15]. Therefore, in current study we evaluated the amounts of these nutrients in our study and control groups.

In the present study, 50 pregnant women with HG were evaluated for demographic features and dietary antioxidant levels and compared with 50 healthy pregnant women. There was no statistically significant difference between the groups regarding age, gravidity, gestational weeks, BMI of the patients and educational status. However, levels of vitamin E, vitamin E equivalent, vitamin A, vitamin C and carotene levels were different between the groups and the difference was statistically significant. The logistic regression method and ROC method also showed that the levels of these nutrients are predictors for HG diagnosis. We used the new 92-item antioxidant nutrient questionnaire developed by Satia to evaluate the antioxidant levels of the patients in this study [1].

Previous studies reported a connection between antioxidant levels and outcomes of different obstetrics conditions in pregnant women. In a meta analysis study, Shah et al., [16] reported that prenatal supplementation with multimicronutrients was associated with lower rate of low-birth-weight infants and with improved birth weight. Spinnato et al., [17] found that supplementation of vitamin C and E reduces the risk of preterm rupture of membranes in pregnant women.

HG is a clinical condition in early pregnancy that includes intractable and treatment-resistant nausea and vomiting, causing electrolyte imbalance, nutritional deficiency and weight loss [1]. The role of some elements in the pathogenesis of HG has been noted in previous reports. Different theories including specific nutrient deficiencies, abnormal lipid levels, changes in the autonomic nervous system, genetic factors, and infection with Helicobacter pylori were discussed in the literature [18-20]. Dokmeci et al., [21] found the plasma zinc levels to be significantly elevated in HG patients. In contrast, Teksen et al., [22] reported that zinc levels were significantly lower in HG patients. To the best of our knowledge, the current study is the first study evaluating antioxidant levels in HG patients. We found that levels of vitamin A, C, E, E equivalent and carotene were significantly lower in patients with HG.

The effect of nutrition in women with HG was described in various studies. Preconceptional multivitamin intake was reported to decrease congenital anomalies and severity of nausea and vomiting during pregnancy [23-25]. Brooks reported that vitamin supplementation such as thiamine, pyridoxine and vitamin C may prevent frequent nausea and vomiting in HG patients [26]. In the current study, we also found the levels of such vitamins reduced in our study group. According to the ROC curve, levels of vitamin E, E equivalent, vitamin C, carotene and vitamin A may be predictive factors of HG.

In conclusion, in patients with pregnancies complicated by HG, we found that levels of vitamin E, E equivalent, vitamin C, carotene and vitamin A were lower when compared with normal pregnancies. This implies that multivitamin intake before and during pregnancy may decrease the severity of HG. Therefore, HG patients should be treated by a team including an obstetrician and dietitian.

References

1. Satia J, Watters J, Galanko J. Validation of an antioxidant nutrient questionnaire in whites and African Americans. *J Am Diet Assoc.* 2009, 109, 502-8, 508.e1-6.
2. Kirk E, Papageorghiou A, Condous G, [et al.]. Hyperemesis gravidarum: is an ultrasound scan necessary? *Hum Reprod.* 2006, 21, 2440-2442.
3. Verberg M, Gillott D, Al-Fardan N, Grudzinskas J. Hyperemesis gravidarum, a literature review. *Hum Reprod Update.* 2005, 11, 527-539.
4. Halvorsen B, Holte K, Myhrstad M, [et al.]. A systematic screening of total antioxidants in dietary plants. *J Nutr.* 2002, 132, 461-471.
5. Halliwell B. Antioxidant defence mechanisms: from the beginning to the end (of the beginning). *Free Radic Res.* 1999, 31, 261–272.
6. Wang Y, Ren W, Liao W, Zhang G. Concentrations of antioxidant vitamins in maternal and cord serum and their effect on birth outcomes. *J Nutr Sci Vitaminol* (Tokyo). 2009, 55, 1-8.
7. Scholl T, Stein T. Oxidant damage to DNA and pregnancy outcome. *J Matern Fetal Med.* 2001, 10, 182-185.
8. Kim Y, Hong Y, Lee K, [et al.]. Oxidative stress in pregnant women and birth weight reduction. *Reprod Toxicol.* 2005, 19, 487-492.
9. Istanbul Program uses data from Bundeslebensmittelschlüssel (BLS) 11.3 and USDA 15. Bebispro for Windows, Germany: Stuttgart, Turkish Version (Bebis 4), 2004.
10. Fairweather D. Nausea and vomiting in pregnancy. *Am J Obstet Gynecol.* 1968, 102, 135–175.
11. Wong K, Leader A, Deitel M. Maternal nutrition in pregnancy. Part II: the implications of previous gastrointestinal operations and bowel disorders. *Can Med Assoc J.* 1981, 125, 550-552.
12. Lin J, Zhang S, Cook N, [et al.]. Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). *Cancer Causes Control.* 2005, 16, 225-233.
13. de Lorgeril M, Salen P, Accominotti M, [et al.]. Dietary and blood antioxidants in patients with chronic heart failure. Insights into the potential importance of selenium in heart failure. *Eur J Heart Fail.* 2001, 3, 661-669.
14. Misso N, Brooks-Wildhaber J, Ray S, [et al.]. Plasma concentrations of dietary and nondietary antioxidants are low in severe asthma. *Eur Respir J.* 2005, 26, 257-264.
15. Sies H, Stahl W, Sundquist A. Antioxidant function of vitamins. *Ann N Y Acad Sci.* 1992, 669, 7-20.
16. Shah P, Ohlsson A, Knowledge Synthesis Group on Determinants of Low Birth Weight and Preterm Births. Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis. *CMAJ.* 2009, 180, 99-108.
17. Spinnato J 2nd, Freire S, Pinto e Silva J, [et al.]. Antioxidant supplementation and premature rupture of the membranes: a planned secondary analysis. *Am J Obstet Gynecol.* 2008, 199, 433.e1-8.
18. Goodwin T. Nausea and vomiting of pregnancy: an obstetric syndrome. *Am J Obstet Gynecol.* 2002, 186, 184-189.
19. Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. *Obstet Gynecol.* 2007, 110, 695-703.
20. Sandven I, Abdelnoor M, Nesheim B, Melby K. Helicobacter pylori infection and hyperemesis gravidarum: a systematic review and meta-analysis of case-control studies. *Acta Obstet Gynecol Scand.* 2009, 88, 1190-1200.
21. Dökmeci F, Engin-Ustün Y, Ustün Y, [et al.]. Trace element status in plasma and erythrocytes in hyperemesis gravidarum. *J Reprod Med.* 2004, 49, 200-204.
22. Tekşen F, Dökmeci F, Kavas G, [et al.]. Copper, zinc and magnesium status in hyperemesis gravidarum. *J Obstet Gynaecol.* 2001, 21, 46-48.
23. Czeizel A, Dudas I, Fritz G, [et al.]. The effect of periconceptional multivitamin-mineral supplementation on vertigo, nausea and vomiting in the first trimester of pregnancy. *Arch Gynecol Obstet.* 1992, 251, 181-185.
24. Källén B, Lundberg G, Aberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. *Acta Obstet Gynecol Scand.* 2003, 82, 916-920.
25. Emelianova S, Mazzotta P, Einarson A, Koren G. Prevalence and severity of nausea and vomiting of pregnancy and effect of vitamin supplementation. *Clin Invest Med.* 1999, 22, 106-110.
26. Brooks M, Melnik G. The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. *Pharmacotherapy.* 1995, 15, 713-726.